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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,172	07/03/2002	Leo Gerardus Joseph Frenken	056159-5041	2740

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EXAMINER

DIBRINO, MARIANNE NMN

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/807,172

Applicant(s)

FRENKEN ET AL.

Examiner

DiBrino Marianne

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 December 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 April 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's amendment filed 12/12/05 is acknowledged and has been entered.

It is noted that the communication filed on 12/12/05 is not fully responsive for the following reason: the specification has not been amended properly under 37 C.F.R.

1.121, which requires that the replacement paragraph(s) must include each replacement paragraph with markings to show the changes relative to the previous version. With regard to the amendment of the paragraph on page 17 beginning at line 15, Applicant has changed "becomes" at line 21 to "became" without marking the deletion or addition, respectively.

2. Applicant is reminded of Applicant's election with traverse of Group I (claim 1 and newly added claim 15), and species of SEQ ID NO: 2 in Applicant's amendment filed 6/27/05.

Upon consideration of the prior art, the search has been extended to include SEQ ID NO: 4, ATTGSSPGPT.

Claims 1 and 15 are currently being examined.

3. For the purpose of prior art rejections, the filing date of the instant claims 1 and 15 is deemed to be the filing date of the 99303008.6 foreign priority document, *i.e.* 4/22/99, as the 9806991 document does not support the claimed limitation "a polypeptide linking group, the amino acid sequence of which group confers restricted conformational flexibility" in the context of the method recited in the instant claims. Only "flexible linkers" is recited in the 9806991 foreign priority document.

The following is a new ground of rejection necessitated by Applicant's amendment filed 12/12/05.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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5. Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghahroudi *et al* (FEBS Letters 1997, Vol. 414, pages 521-526) in view of Alfthan *et al* (Protein Eng. 1995, 8(7): 725-731, IDS reference).

Ghahroudi *et al* teach "Considering the single domain nature of the cAbs," *i.e.*, the Camelid VH antigen binding domains, "it should be straightforward to construct small bivalent or even multivalent binders...in order to increase their avidity. Also, the generation of bispecific constructs can be envisaged to broaden the potential applications of camel single domain antibodies... In all cases, the resulting molecules will always be simpler, smaller, and probably more stable than the corresponding derivatives of scFvs or Fabs." (especially last paragraph of article on page 525).

Ghahroudi *et al* are silent as to the method of producing bivalent or multivalent VH antibodies.

Alfthan *et al* teach a method of making bivalent or higher order valency scFv antibodies using the linking peptide ATTGSSPGPT, and teach that it is advantageous to use this 11-mer linker because it drives dimerization or multimerization of single chain antibody fragments (SEQ ID NO: 4 of instant claim 1). Alfthan *et al* teach the use of a number of proline-containing (inflexible) linkers. Alfthan *et al* teach that the tendency to produce dimers and multimers is shared among many different single chain antibodies (see entire reference, especially abstract, first full paragraph at column 2 on page 725, paragraph spanning pages 725-726, Figure 1A, last two paragraphs of article on page 730).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made bivalent or multivalent VH antibodies as per the teaching of Ghahroudi *et al* using the method taught by Alfthan *et al* using the ATTGSSPGPT linker peptide.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to product a higher valency antibody to increase the avidity of VH camelid antibodies and to increase their range of applicable use as taught by Ghahroudi *et al*, and to use the method taught by Alfthan *et al* involving linkage of the individual binding units using the ATTGSSPGPT peptide, particularly in light of the teaching of Ghahroudi *et al*, that the VH antibodies lend themselves to straightforward construction of dimers or multimers and that they will be superior to scFv, another small antibody fragment, in that they are smaller, simpler and probably more stable, and the teaching of Alfthan *et al* that the tendency to produce dimers and multimers is shared among many different single chain antibodies and that it is advantageous to use the ATTGSSPGPT linker peptide to achieve this purpose.

6. No claim is allowed.

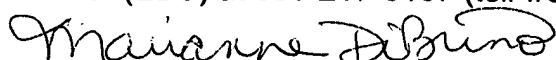
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7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.


8. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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February 6, 2006



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